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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,754	ALLEN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-26,28-30,32 and 36-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-26,28-30,32 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 March 2005 has been entered.

This Office Action is a reply to the 21 March Paper in response to the Final Office Action mailed 21 December 2004. Claims 24-26, 28-30, 32 and 34-40 were considered in the 21 December Office Action. Claims 24-26, 32, 37 and 39 were amended and claims 34, 35 and 40 were canceled in the 21 March Paper. Claims 24-26, 28-30, 32 and 36-39 are pending and under consideration.

Response to Amendment and Arguments

Rejection of claims 35 and 40 is rendered moot by cancellation of the claims.

Claim Rejections - 35 USC § 101/§112, first paragraph

Claims 24-26, 28-30, 32 and 36-39 stand rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial credible asserted utility or a well-established utility.

Applicant's arguments have been fully considered but are not deemed persuasive.

Applicant first reiterates arguments previously submitted in the Paper filed 14 October 2004. Applicant argues that the Patent Office guidelines state that an asserted utility should be presumed to be true (page 6-8). Applicant further asserts that the well-known use of the claimed mouse is in characterizing the function of the mTMT gene that has been deleted therefrom. Applicant cites excerpts from an NIH website, Austin *et al.*, Lewin, Joyner, Matise and Albert's Molecular Biology of the Cell in establishing that knockout mice are invaluable tools of scientific research (pages 8-10). Applicant also cites the MPEP in discussing the utility of research tools (page 9 of the 21 March Paper and MPEP 2107.01,I). In general, Applicant does not understand how the invention cannot have utility when knockout animals are used by those of skill in the art and have been accepted as useful by several leaders in the field of transgenic technology.

In response, the instant invention fails to meet the requirements for a well-established or asserted specific and substantial credible utility. A well-established utility and a utility with a particular practical purpose is one that is specific and substantial. With respect to the references cited by Applicant, the validity of the opinion of the NIH and Bruce Albert is not questioned. However the use of a mouse to determine the function of a gene deleted from the mouse as asserted by Applicant is not a specific and substantial patentable utility. Applicant cannot rely on general statements as to the value of transgenic animals as objects of basic research to establish a specific utility for the animal of the instant claims. Furthermore, as discussed in the previous Office Action, with regard to "substantial utilities", MPEP 2107.01 states, "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use and, therefore, do not define 'substantial

utilities': (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved...(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility..." In *Brenner, Comr. Pats. v. Manson,* 148 USPQ 689 (US SupCt 1966), the Supreme Court found that there is a distinction between scientific utility, which is evidenced in the articles cited by Applicant, and patentable utility under 35 USC §101. The Court states, "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing...This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short of the invention of something 'useful', or that we are blind to the prospect that what now seems without 'use' may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful completion" (page 696).

In the 21 March Paper, Applicant responds to these arguments by asserting that the utility is specific because "1) the specification describes specifically why the invention is useful; and 2) the specification discloses specific biological properties reasonably correlated to a disease condition" (paragraph bridging pages 13-14). In that same paragraph, Applicant goes on to state, "[t]his is not a case wherein Applicant has generally discussed a utility that may arise, but has asserted that the invention is useful for investigating the function of the mTMT gene, particularly as it relates to the phenotypes claimed."

However, as discussed in the Office Action mailed 16 July 2004, with regard to the utility of the claimed mouse and cells as a disease model, it is first noted that the phenotypic differences identified in mice comprising a homozygous disruption of an endogenous mTMT gene relative

to wild-type mice are very small and do not appear to be statistically significant (see especially Figures 3-5). Given that phenotype of the claimed mouse is statistically the same as that of a wild-type mouse, it logically would not be possible to establish a statistically significant amelioration of those differences. Thus, additional experimentation is required to reasonably establish that the phenotypic differences asserted in the application are of sufficient magnitude to be useful as a model. Furthermore, even if the phenotype of the claimed mouse were significantly different from a wild-type mouse, neither the specification nor the art provides a specific and substantial teaching of what disease state is modeled by the animal. All of the teachings in the specification regarding the utility of the claimed animal as a disease model are general in nature and would apply to any transgenic animal exhibiting an altered phenotype. Although the specification discloses that the mouse exhibits decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio and increased pre-pulse inhibition, all relative to wild-type mice, there is no teaching what specific disease state is being modeled. The specification asserts that the transgenic animals and cells may be utilized as models for diseases, disorders, or conditions associated with phenotypes relating to a disruption in a tryptase, but provides no specific teaching as to what diseases, disorders, or conditions relate to a disruption in a tryptase. As established in the Office Action mailed 10 May 2002, the phenotype arising from disruption of any given gene in any given animal is highly unpredictable (see especially the discussion beginning in the first full paragraph on page 7). Therefore, it cannot be asserted the phenotypic characteristics disclosed for the claimed mouse are relevant to any other species of mammal comprising a disruption in an endogenous mTMT gene without additional experimentation to reasonably confirm that this is the case. Thus, the utility asserted for the

claimed animal is neither specific, because the specification fails to identify the specific disease state modeled by the animal, nor substantial, because it is merely an invitation to the skilled artisan to experiment and identify which, if any, diseases are modeled by the claimed invention.

Applicant's assertion that the invention is useful for investigating the function of the mTMT gene as it relates to the phenotypes claimed is clearly not a substantial utility. First, as stated in the previous Office Action, page 6, using the mouse to define the function of the gene knocked-out from the mouse is not a substantial utility because it amounts to using the animal as an object of use-testing. Beyond contributing to the fund of scientific knowledge, the only purpose of determining the functional properties of the mTMT gene is to discover a 'real-world' utility for the mouse or the gene. In the section bridging pages 14-15 of the response, Applicant asserts that this argument is based on an improper application of the MPEP definition of "substantial utility". Applicant cites MPEP §2107.01, I and urges:

> The portions of the MPEP guidelines referred to by the Examiner relate to the situation where further research is required to establish or confirm **any utility**. As acknowledged by the Examiner in the instant Office Action, knockout mice have a well-known use to study gene function (citing Smyth[]). In the present case, the present invention does not require further research to establish a utility. Applicant has determined that the mTMT gene is associated with prepulse inhibition, a deficit in which a strongly associated with schizophrenia (in humans) as well as with abnormal body weight or weight gain" (emphasis in original; citations omitted).

Applicant is reminded that the Examiner's position on substantial utility is based upon the passages cited from MPEP §2107.01 and the case law *Brenner, Comr. Pats. v. Manson,* 148 USPQ 689 (US SupCt 1966), wherein the Supreme Court found that there is a distinction between scientific utility and patentable utility under 35 USC §101 (*Id.*). It is acknowledged that the invention being claimed is the mouse and not the gene which applicant proposes to characterize. However, there is no question that what applicant proposes to be a patentable utility

is actually basic research to obtain information about the properties of the mouse itself. Applicant appears to be asserting that such a utility is substantial because the information obtained might be used, after considerable additional research to establish how what is measured in the mouse is related to the gene, to understand the properties of an mTMT gene. However, beyond contributing to the fund of scientific knowledge, which the Supreme Court found to be insufficient to support a patentable utility, the only purpose of determining the functional properties of the mTMT gene is to discover a 'real-world' utility for the mouse or the gene. This is not a patentable utility.

With regard to Applicant's assertion that the mTMT gene is associated with prepulse inhibition, abnormal body weight or weight gain, as discussed in the Office Action mailed 16 July 2004 (pages 4-6) and herein above, that the phenotypic differences identified in mice comprising a homozygous disruption of an endogenous mTMT gene relative to wild-type mice do not appear to be statistically significant. Thus, additional experimentation is required to reasonably establish that the phenotypic differences asserted in the application are of sufficient magnitude to be useful as a model. Furthermore, even if the phenotype of the claimed mouse were significantly different from a wild-type mouse, neither the specification nor the art provides a specific and substantial teaching of what disease state is modeled by the animal. With regard to pre-pulse inhibition, the specification teaches that the mice exhibit "a stimulus processing phenotype opposite to that seen in schizophrenic patients" (page 53), which is not recognized as a useful model of anything. Thus, the utility asserted for the claimed animal is neither specific, because the specification fails to identify the specific disease state modeled by the animal, nor

substantial, because it is merely an invitation to the skilled artisan to experiment and identify which, if any, diseases are modeled by the claimed invention.

In response to the Examiner's assertion that a mouse comprising a disrupted allele is not necessarily useful to study the function of the disrupted gene, Applicant cites teachings from Olsen, which indicate that knockout mice have proved valuable in understanding the roles of GAD and GABAR. Applicant urges, "it is untenable to cite Olsen as standing for the proposition that knockout mice do not have a well accepted use" (page 17). However, it was never asserted that Olsen teaches that knockout mice do not have an accepted use. It was asserted that the utility of any given mouse for studying the properties of any given gene is not a certainty. The Office has never held the position that the utility asserted by Applicant is not credible; however, given the unpredictable nature of the art, the utility of any given transgenic animal must be established individually and, therefore, is not substantial. Applicant is again reminded that the relationship of the phenotype displayed by a mouse comprising a mutation in any given gene is highly dependent on genetic background. This fact is well known to one of ordinary skill in the art. For example, Gerlai *et al.* (1996) *Trends Neruosci.* 19:177-181, 177 teaches:

> The functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Clearly, a null-mutant organism might not only lack the product of a single gene but might also possess a number of developmental, physiological, or even behavioral processes that have been altered to compensate for the effect of the null mutation. Therefore, one might expect an array of complex phenotypical changes that might not be directly related to the function of the gene of interest. Teasing out the primary and secondary changes will require co-ordinated efforts of scientists from several fields of biology. However, these efforts might be conduced in vain if the effects of genes other than those of the one targeted have not been ruled out with certainty.

Thus, while there is no question that transgenic animals, as a class of invention, can be used to study genes (although this by itself is not a patentable utility), the utility of any given transgenic animal must be established independently.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §101 as lacking a patentable utility and 35 USC §112, first paragraph, as lacking an enabling disclosure.

Claim Rejections - 35 USC § 112

Rejection of claim 32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment thereto.

Rejection of claim 29 under 35 USC §112, second paragraph as indefinite in reciting in step (b), "the pseudopregnant mouse generates" is withdrawn in view of the amendment thereto.

Claim Rejections - 35 USC § 103

Rejection of claims 24, 36 and 37 under 35 U.S.C. 103(a) as being unpatentable over Wong *et al.* and Smyth *et al.* in view of Capecchi is withdrawn in view of the limitation of the claimed mouse to exhibiting a specific phenotype.

Claims 29, 30 and 32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wong *et al.* and Smyth *et al.* in view of Capecchi.

In response to the *prima facie* case of record, Applicant argues that the cited art is deficient in the requirements for a *prima facie* case of obviousness because the art fails to teach a transgenic mouse whose genome comprises a null mTMT allele, wherein the transgenic mouse exhibits a decreased body weight; decreased thymus weight; decreased thymus weight to body weight ratio; or increased prepulse inhibition, methods of producing the mouse and targeting constructs used to produce the null allele.

Applicant's arguments have been fully considered but are not deemed persuasive. The claims which stand rejected are directed to a method of producing a mouse having the properties of the mouse of claim 24, a targeting construct used to produce the mouse and a mouse embryonic stem cell whose genome comprises a null endogenous mTMT allele.

As stated in the previous Office Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wong *et al.* and Capecchi as claimed in the instant claims 29 and 30 to produce a knockout mouse as suggested by Smyth *et al.* The art teaches each of the elements of the targeting construct of claim 30 and the method of producing a knockout mouse of claim 29, and one would be motivated to combine these teachings in view of the teachings from Smyth *et al.* Absent evidence to the contrary, the property of providing a null allele is inherent to the knockout technology disclosed in the art. Although the phenotypic properties of the mouse itself are unpredictable and, therefore, unexpected, the process steps recited in claim 29 are no different from those taught in the art. Therefore, the claimed method of making a mouse is obvious over the art.

Likewise, the elements of the targeting construct of claim 30 remain obvious in view of the cited art for the reasons set forth in the previous Office Action. The "wherein" clause inserted into part (d) does not distinguish the targeting construct from the art because it is reciting properties which, absent evidence to the contrary, are inherent to any targeting vector constructed to knockout an mTMT allele. The phenotype of a transgenic animal is unpredictable because it is determined by the genetic background of the mutation as well as the mutation itself. Any targeting vector having the structural features set forth in claim 30 will produce a mouse comprising a null allele and exhibiting the phenotypic characteristics recited in the claim if inserted into the proper genetic background. Therefore, reciting those properties does not distinguish the claim from the art.

Finally, the embryonic stem cell of claim 32 is not limited to exhibiting any particular phenotype. As described in the previous Office Action, the art suggests that it is desirable to make a transgenic animal comprising a knockout of the mTMT gene and teaches a process of making an mTMT gene which, absent evidence to the contrary, would include providing a mouse embryonic stem cell whose genome comprises a null endogenous mTMT allele.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 USC §103(a) as obvious over the art.

New Grounds

Specification

The amendment filed 21 March 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant has amended the specification at page 10, paragraph 4, to incorporate several applications and an issued patent that had not previously been incorporated. As these disclosures were not incorporated by reference at the time of filing, their incorporation by amendment constitutes impermissible new matter added to the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-26, 28-30, 32 and 36-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not

limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

First, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Furthermore, even if one were to accept Applicant's assertions that the disclosure satisfies the utility requirement of 35 USC §101, the skilled artisan would not be able to use the invention as asserted by applicant without first engaging in undue experimentation.

Nature of the invention and Breadth of the claims: The claims are directed to a transgenic mouse comprising a homozygous disruption in an endogenous mTMT gene, wherein the transgenic mouse exhibits a phenotype selected from decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio and increased pre-pulse inhibition, to a cell or tissue isolated from the transgenic mouse and to a method of producing the transgenic mouse. All of the teachings in the specification regarding how one might use a transgenic animal comprising the recited genotype and phenotype, and cells or tissues derived therefrom, are based on the assertion that the animal and cells are models for disease. For example, on page 18, first full paragraph, the specification teaches, "[t]he cell- and animal-based systems described herein can be utilized as models for diseases" and "the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions that may be effective in treating

disease." In the second full paragraph on page 18, the specification teaches, "cells are examined to determine whether one or more of the disease cellular phenotypes has been altered to resemble a more normal or more wild type, non-disease phenotype." On page 19, lines 28-30, the specification teaches, "[t]he transgenic animals and cells of the present invention may be utilized as models for diseases, disorders, or conditions associated with phenotypes relating to a disruption in a tryptase." In addition, Applicant asserts that the claimed invention has well-established utility to study the function of the mTMT gene. In view of these asserted utilities, it is incumbent upon the application disclosure to teach the skilled artisan how to use the claimed animal as a model for disease or to study the function of the mTMT gene in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the animal for those purposes without undue experimentation.

Amount of direction provided by the inventor and existence of working examples: The working examples teach introduction of a tryptase targeting construct into 129/sv-+P+Mgf-SLJ/J mouse ES cells and generation of chimeric mice, which were then bred with C57BL/6 females to produce F1N0 heterozygous mice. F1N0 heterozygotes were either intercrossed to produce F2N0 homozygotes or backcrossed to C57BL/6 mice to generate F1N1 heterozygotes. F2N1 homozygous mutant mice were produced by intercrossing F1N1 heterozygous males and females (page 51). The homozygous mice were found to exhibit statistically insignificant differences in average body weight (Figure 3 and page 51), reduced thymic weight and thymus to body weight ratio (Figure 4 and page 52), and an increase in prepulse inhibition all relative to a wild-type, presumably littermate, control.

The specification also provides generic teachings regarding using transgenic animals and cells derived therefrom as disease models. The specification teaches that cell-based systems may be used to identify compounds that act to ameliorate disease symptoms by determining whether one or more disease cellular phenotype has been altered to resemble a more normal or more wild-type, non-disease phenotype (page 18). Likewise, the specification teaches that animal based systems can be used for the identification pharmaceuticals and outlines a variety of neurological tests that can be used in drug screens (page 19-26).

However, the teachings provided in the application fall well short of providing an enabled animal model of any disease. First, the specification fails to provide any information as to the genotype of the mice used in the experiments other than it is established from cells that were transfected with a targeting construct. In particular, the specification does not teach whether or not the mice comprise a null mutation of the mTMT gene as recited in the claims. Thus it is not clear from the specification whether a mouse whose genome comprises a null endogenous mTMT allele would exhibit the phenotypes recited in the claims. Furthermore, the phenotypic differences identified in mice comprising a homozygous disruption of an endogenous mTMT gene relative to wild-type mice are very small and do not appear to be statistically significant (see especially Figures 3-5). Given that phenotype of the claimed mouse is statistically the same as that of a wild-type mouse, it logically would not be possible to establish a statistically significant amelioration of those differences. Thus, additional experimentation is required to reasonably establish that the phenotypic differences asserted in the application are of sufficient magnitude to be useful as a model. Likewise, as the disclosure fails to teach any phenotype at all

for the claimed cell or tissue, the skilled artisan would have to experiment to determine how to use the cell to screen for drugs.

Still further, even if the phenotype of the claimed mouse were significantly different from a wild-type mouse, neither the specification fails to teach of what disease state is modeled by the animal. All of the teachings in the specification regarding the utility of the claimed animal as a disease model are general in nature and would apply to any transgenic animal exhibiting an altered phenotype. Although the specification discloses that the mouse exhibits decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio and increased pre-pulse inhibition, all relative to wild-type mice, there is no teaching of what specific disease state is modeled. Does the decreased body weight represent a metabolic disorder? If so, which one? What, precisely, is being modeled by a decreased thymus weight to body weight ratio? The specification teaches that the mice exhibit a stimulus processing phenotype opposite to that seen in schizophrenic patients (page 53). What medical condition is modeled by a phenotype opposite to that seen in schizophrenic patients? The specification asserts that the transgenic animals and cells may be utilized as models for diseases, disorders, or conditions associated with phenotypes relating to a disruption in a tryptase, but leaves to the skilled artisan the task of determining what, if any, diseases, disorders, or conditions relate to a disruption in a tryptase.

With regard to using the mouse and cells to study the function of the mTMT gene, the specification fails to establish how any given characteristic of the claimed invention is related to the properties of mTMT gene such that the skilled artisan could use the mouse or cells derived therefrom to study the mTMT gene without undue experimentation to adequately characterize the invention.

State of the prior art and level of predictability in the art: The art available at the time of filing teaches that correlating any given phenotypic characteristic in a knockout mutant mouse with the functional characteristics of the ablated gene or with a disease state was highly unpredictable. In attempting to determine gene function through an analysis of behavioral or physiological testing of mice comprising a disruption of a gene, distinguishing between a phenotype that is a result of gene loss and genes of the parental strains becomes problematic. In the production of the presently claimed mice, the specification, as outlined above, states that the recombination construct is injected into a 129/sv-+P+Mgf-SLJ/J mouse ES cell which were used to produce mice on a C57BL/6 background. Wolfer *et al.* (2002) *TRENDS Neurosci.* 25 :336-340 teaches that mice created this way will comprise not only the induced null mutation, but also 129 genes from the ES cells. Furthermore, a linkage disequilibrium will exist for genes linked to the target gene because animals comprising the target gene will also comprise the linked 129-derived alleles and mice that do not comprise the target gene will comprise alleles of the background strain. Thus, without experimental characterization of the animal, the skilled artisan does not know which phenotypic characteristics are a result of the target gene ablation and which are a result of linkage disequilibrium of genes linked to the target gene.

Furthermore, even if a phenotypic characteristic is a consequence of ablation of the target gene, the relationship of the phenotype to the genotype must be established before useful information about the function of the target gene can be obtained. Gerlai (*supra*) teaches that the functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Gerlai teaches, "a null-mutant organism might not only lack the

product of a single gene but might also possess a number of developmental, physiological, or even behavioral processes that have been altered to compensate for the effect of the null mutation. Therefore, one might expect an array of complex phenotypical changes that might not be directly related to the function of the gene of interest. Teasing out the primary and secondary changes will require co-ordinated efforts of scientists from several fields of biology. However, these efforts might be conduced in vain if the effects of genes other than those of the one targeted have not been ruled out with certainty" (page 177). Thus, Gerlai clearly teaches that knowledge of a phenotype is not sufficient to enable study of gene function without additional information as to whether and how a given phenotypes can be used as an indicator of a genes function.

With regard to modeling disease, the art does not teach the association of the mTMT gene with any disease state and the examiner can find no teaching in the art or the instant specification as to what diseases are being modeled by the phenotypes recited in the claims. Furthermore, it is well established that the phenotype exhibited by an animal comprising a homozygous ablation of a given gene is highly dependent upon genetic background. This is illustrated by Crawley (1996) *TRENDS Neurosci.* 19:181-182, who provides an example of a knockout of the *HEXA* gene, which in humans results in Tay-Sachs disease but produces no ill-effects in mice (see especially the paragraph bridging page 180-181). Thus, even if one could reasonably assert that the phenotypes displayed by the claimed mouse constitute a disease state, it is unclear, without additional experimentation, how that state is relevant to any organism other than the mouse itself.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill would not be able to use the animals or cells claimed without undue experimentation. Given the

unpredictable nexus of genotype and phenotype in knockout mice and the unpredictability of correlating the phenotypic characteristics of a gene knockout in a mouse with any given disease state, using the claimed invention as a disease model or to study the function of the mTMT gene as asserted would require undue experimentation. The art teaches that the phenotype exhibited by a knockout mouse might be a consequence of developmental, physiological, or even behavioral processes that have been altered to compensate for the effect of the null mutation, or might be related to the target mutation only as a consequence of disequilibrium of genes linked to the target gene. Thus, using the mouse to study the gene requires that the skilled artisan first establish that the phenotype is actually related to the functional properties of the gene and how phenotype and function are related. The art also teaches that the characteristics of an animal comprising a mutation in a target gene are highly dependent upon genetic background. Thus, the relevance of information obtained using a given knockout mouse to any organism other than the mouse itself must be carefully established before the animal can be used as a disease model. Therefore, using the mouse as asserted would require undue experimentation.

With regards to the claims to cells obtained from the mouse, the cells would not exhibit the phenotypic characteristic disclosed for the mouse and no phenotype has been disclosed for the cells. Thus, in addition to experimenting to identify a disease state modeled by the cells, the skilled artisan would have to experiment to determine a phenotype that could be used to screen for therapeutic agents as contemplated in the specification.

Finally, as the mouse and cells do not have an enabled use, products and methods used to make the mouse lack an enabled use.

For these reasons, the skilled artisan would not be able to use the claimed invention as asserted by applicant without first engaging in undue experimentation to further develop what is claimed. Therefore, the claims are properly rejected under 35 USC §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 28-30, 32 and 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24 and 30 are indefinite in reciting that the phenotypes exhibited by the animal are decreases or increases in various parameters without specifying a benchmark against which the increase or decrease is established. For example, a the same transgenic mouse might exhibit a decreased body weight relative to one strain of mouse and an increased body weight relative to another strain of mouse. Given that the same mouse might be both inside and outside the scope of the claim it is not possible to ascertain what is covered by the claim.

Claims 28, 29, 32 and 36-39 are indefinite insofar as they depend from claim 24 or 30.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner
Art Unit 1636